## REMARKS

Reconsideration and allowance are respectfully requested.

Claims 18-19 and 22-32 are pending. The rejoinder of withdrawn claims 30-32, which are directed to methods of using and processes for making, is requested upon allowance of the elected product claim 21. A typographical error in the dependency of claim 32 is corrected.

The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. No new issues are raised by amendment of claims 18-19, which merely incorporate limitations previously presented in claims 1 and 10 from which claims 18-19 used to depend. The unit dose form of claims 18-19 is a 50 µg or 100 µg tablet, which refers to the amount of active ingredient per unit dose form (see page 4, line 27, of the specification). These are nominative amounts because a "50 µg tablet" actually contains 0.0425-0.0575 mg levothyroxine sodium (based on page 4, line 29, of the specification) and a "100 µg tablet" actually contains 0.085-0.115 mg levothyroxine sodium (based on page 4, lines 31-32, of the specification). Similarly, no new issues are raised by amendment of claim 21, which should be entered to address the Examiner's new matter rejection. It could not be previously presented because that rejection was initially raised in the final Office Action. Moreover, a water content of 3 to 6% based upon total weight of the formulation was a limitation previously recited in dependent claim 24; the Office Action stated this specific range was disclosed in Applicants' specification. Thus, no additional search or consideration by the Examiner is required for the proposed claim amendments. Their entry will reduce the issues on appeal.

### *Statement of the Substance of the Interview*

The undersigned acknowledges the courtesy of the Examiner during the interview on July 15, 2010. Proposed claim amendments and the prior art were discussed. An amendment adopting the Examiner's suggestion in the final Office Action to recite "3-6%" would overcome the new matter rejection. He was not, however, persuaded that this limitation to the water content by itself would overcome the obviousness rejection. Not discussed during the interview were the arguments below about the other indepen-

dent bases for nonobviousness that are recited in the pending claims. The foregoing is Applicants' summary of the interview. If anything else is required to complete the record, do not hesitate to contact the undersigned.

*35 U.S.C. 112 – Written Description*

Claim 21 was rejected under Section 112, first paragraph, because the phrase "a water content of at least 3% " is allegedly not supported by the specification as originally filed. Applicants traverse because the challenged limitation is modified to indicate an upper limit of 6%. The present range of water content would be recognized by a skilled person as in Applicants' possession when this application was filed. Support for "a water content of 3 to 6% w/w based upon total weight of the formulation" is found on page 3, line 2, of the specification. The present amendment incorporates in independent claim 21 a limitation previously recited in dependent claim 24.

Therefore, withdrawal of the written description rejection is requested because the objection to "at least 3%" is mooted by amendment of claim 21.

*35 U.S.C. 103 – Nonobviousness*

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie

case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. A claim directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-11, 18-29 and 33-34 were rejected under Section 103(a) as allegedly unpatentable over MITRA (US 5,955,105) as evidenced by HANDBOOK (*Handbook of Pharmaceutical Excipients, 5th Ed.*, pp. 134, 725 and 731-732, 2006) and MSDS (Material Safety Data Sheet, L-Thyroxine, sodium salt) in view of EUROPEAN PHARMACOPOEIA (pp. 1438 and 2002) and FRANZ et al. (US 2003/0032675). Applicants traverse.

Applicants' claims 18-19 are directed to pharmaceutical formulations in unit dose form and containing specific amounts of their components. They all require microcrystalline cellulose which has a mean particle size of less than 125 µm. More generally, claim 21 is directed to pharmaceutical formulations, which comprise:

(a) an effective amount of levothyroxine sodium,

(b) microcrystalline cellulose having a mean particle size of less than 125 µm and present in an amount of 60 to 85% w/w, and

(c) pregelatinised starch present in an amount of 5 to 30% w/w which is produced by subjecting moistened starch to mechanical pressure in order to rupture some or all of its starch granules and subsequent drying;

wherein the pharmaceutical formulation has a water content of 3 to 6% w/w based upon total weight of the formulation. None of these pharmaceutical formulations is disclosed or rendered obvious by the cited documents.

Claims 18-19 and 21 require microcrystalline cellulose having a mean particle size of less than 125 µm. Applicants have shown in their specification (Example 2) that this limitation confers the advantage of stabilising their claimed formulations in (B) on pages 7 and 9, where the effect of microcrystalline cellulose particles size on levothyroxine sodium tablets was analysed: "The data shows (sic) that a higher levothyroxine sodium content is maintained and the total impurities are lower when microcrystalline

cellulose with a mean particle size of 50 µm or 100 µm compared to 180 µm is used in the levothyroxine sodium formulation" (page 7, lines 33-35, of the specification). Therefore, the aforementioned limitation requiring microcrystalline cellulose having a mean particle size of less than 125 µm provides the unexpected results of maintaining higher levothyroxine sodium content and lowering the total impurities for the claimed pharmaceutical formulations. These advantages were not taught or suggested in the prior art. This is an independent basis for patentability from the stabilising effect obtained by "a water content of 3 to 6% w/w based upon total weight of the formulation" (claim 21).

MITRA discloses stabilised pharmaceutical preparations containing levothyroxine sodium. Stabilisation was achieved using a water-soluble glucose polymer (e.g., maltodextrins at column 4, lines 15-16), and a partially soluble or insoluble cellulose polymer (see claim 1). Example 10 of MITRA used microcrystalline cellulose as partially soluble or insoluble glucose polymer, and starch as water-soluble glucose polymer. But MITRA is silent on the advantage of requiring the microcrystalline cellulose to have a mean particle size of less than 125 µm, which is a requirement of the pending claims even if the proposed amendments are not entered.

Applicants' claimed invention requires microcrystalline cellulose having a mean particle size of less than 125 µm, which was demonstrated to have certain advantages. These advantages of maintaining a higher levothyroxine sodium content and lowering the total impurities were not taught or suggested in the prior art, nor would they have been obvious to one of ordinary skill in the art with a reasonable expectation of success. Further, optimization of mean particle size to increase stability of a levothyroxine formulation was not taught or suggested by the evidence of record.

The failure of MITRA to disclose the claimed invention is not remedied by the Examiner's attempt to combine its disclosure with MSDS, EUROPEAN PHARMACOPOEIA, and FRANZ. Applicants' claims differ from what is disclosed by requiring the microcrystalline cellulose to have a mean particle size of less than 125 µm. Neither MSDS nor EUROPEAN PHARMACOPOEIA is relevant to microcrystalline cellulose and its mean particle size. FRANZ discloses formulations containing microcrystalline cellulose but, like MITRA, the '675 application is silent on any relationship between mean

particle size and stability. For example, "Sifting segregation can occur with a mean particle size in the 50 micron range and can become a dominant segregation mechanism if the mean particle size is above 100 microns" (paragraph [0033]) does not make obvious a mean particle size of less than 125 µm for microcrystalline cellulose. In fact, it teaches away the mean particle sizes of 50 µm and 100 µm that were successfully used in Applicants' Example 2. Moreover, Applicants' data show that a mean particle size of less than 125 µm is critical for stabilising their claimed pharmaceutical formulation. It is not the expected outcome of routine optimization.

Further experiments have been performed that were not in Applicants' specification. They evaluate the effects of changing the carrier on stability. A triturate composition of 2.5% w/w levothyroxine sodium in the carrier was selected. Microcrystalline cellulose of various mean particle sizes were evaluated for their suitability as carriers.

Triturates samples were prepared and stored under conditions of 60°C/ambient humidity and 40°C/75% RH for 14 days. The samples were assessed for stability (assay of levothyroxine sodium) and content uniformity of active ingredient (sampled in earlier fixed places). All content uniformity results and stability results are summarised in the following Tables 1 to 7.

Table 1. Batch 010201RB – carrier Cellulose Microcrystalline grade 101

| Sample | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---|---|---|---|
| 1 | 2.46 (98.4) | 2.38 | 2.38 |
| 2 | 2.39 (95.6) | 2.39 | 2.33 |
| 3 | 2.41 (96.4) | | |
| 4 | 2.41 (96.4) | | |
| 5 | 2.40 (96.0) | | |
| 6 | 2.42 (96.8) | | |
| Mean | **2.42 (96.8)** | **2.38 (98.5)** | **2.35 (97.2)** |
| RSD (%) | **1.0** | | |

Table 2. Batch 050401RB – carrier Cellulose Microcrystalline grade 101

| Sample | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---|---|---|---|
| 1 | 2.55 (102.0) | 2.35 | 2.35 |
| 2 | 2.47 (98.8) | 2.39 | 2.39 |
| 3 | 2.46 (98.4) | | |
| 4 | 2.44 (97.6) | | |
| 5 | 2.43 (97.2) | | |
| 6 | 2.47 (98.8) | | |
| Mean | **2.47 (98.8)** | **2.37 (95.9)** | **2.37 (95.9)** |
| RSD (%) | **1.66** | | |

Table 3. Batch 030401RB – carrier Cellulose Microcrystalline grade 102

| Sample | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---|---|---|---|
| 1 | 2.68 (107.2) | 2.46 | 2.38 |
| 2 | 2.52 (100.8) | 2.48 | 2.42 |
| 3 | 2.52 (100.8) | | |
| 4 | 2.52 (100.8) | | |
| 5 | 2.52 (100.8) | | |
| 6 | 2.56 (102.4) | | |
| Mean | **2.55 (102.0)** | **2.47 (96.7)** | **2.40 (94.2)** |
| RSD (%) | **2.56** | | |

Table 4. Batch 040401RB – carrier Cellulose Microcrystalline grade 102

| Sample | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---|---|---|---|
| 1 | 2.60 (104.0) | 2.52 | 2.41 |
| 2 | 2.59 (103.6) | 2.48 | 2.40 |
| 3 | 2.55 (102.0) | | |
| 4 | 2.56 (102.4) | | |
| 5 | 2.62 (104.8) | | |
| 6 | 2.58 (103.2) | | |
| Mean | **2.58 (103.2)** | **2.50 (96.9)** | **2.40 (93.2)** |
| RSD (%) | **0.98** | | |

Table 5. Batch 010701RB – carrier Cellulose Microcrystalline grade 103

| Sample | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---|---|---|---|
| 1 | 2.49 (99.6) | 2.38 | 2.27 |
| 2 | 2.36 (94.4) | 2.36 | 2.31 |
| 3 | 2.45 (98.0) | | |
| 4 | 2.48 (99.2) | | |
| 5 | 2.50 (100.0) | | |
| 6 | 2.47 (98.8) | | |
| Mean | **2.46 (98.4)** | **2.37 (96.3)** | **2.29 (93.1)** |
| RSD (%) | **2.05** | | |

Table 6. Batch 010401RB – carrier Cellulose Microcrystalline grade 200

| Sample | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---|---|---|---|
| 1 | 2.70 (108.0) | 2.26 | 2.33 |
| 2 | 2.75 (110.0) | 2.26 | 2.23 |
| 3 | 2.63 (105.2) | | |
| 4 | 2.63 (105.2) | | |
| 5 | 2.65 (106.0) | | |
| 6 | 2.61 (104.4) | | |
| Mean | **2.66 (106.4)** | **2.26 (84.9)** | **2.28 (85.7)** |
| RSD (%) | **1.95** | | |

Table 7. Batch 020401RB – carrier Cellulose Microcrystalline grade 200

| Sample | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---|---|---|---|
| 1 | 2.56 (102.4) | 2.29 | 2.22 |
| 2 | 2.41 (96.4) | 2.36 | 2.13 |
| 3 | 2.45 (98.0) | | |
| 4 | 2.64 (105.6) | | |
| 5 | 2.52 (100.8) | | |
| 6 | 2.51 (100.4) | | |
| Mean | **2.51 (100.4)** | **2.33 (92.5)** | **2.18 (86.5)** |
| RSD (%) | **3.27** | | |

Note microcrystalline cellulose Grades 101, 102 and 103 have a mean particle size of 50-100 μm while microcrystalline cellulose Grade 200 has a mean particle size of 180 μm. The above results reinforce the improved stability of formulations containing microcrystalline cellulose having a mean particle size of less than 125 μm.

One of ordinary skill starting from a prior art formulation would not have found it obvious to limit the mean particle size of the microcrystalline cellulose and would not have a reasonable expectation that this change would provide the surprising result that the modified formulation maintains a higher levothyroxine sodium content and lowers the total impurities.

Further, dependent claims 22-29 are patentable over MITRA in view of MSDS, EUROPEAN PHARMACOPOEIA, and FRANZ because their combined disclosures do not render obvious all limitations of independent claim 21. In other words, claims 22-29 are not obvious from the cited documents because the limitations of the independent claim are incorporated in its dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

In summary, the cited documents fail to make obvious Applicants' claimed pharmaceutical formulations. In particular, no evidence was presented in the Office Actions that one of ordinary skill in the art would have limited the mean particle size of microcrystalline cellulose with a reasonable expectation that the formulations' stability would be improved. Therefore, Applicants' claimed invention would not have been obvious from the cited documents.

Finally, claims 18-19 require additional limitations to specific amounts of levothyroxine sodium, microcrystalline cellulose having a mean particle size of less than 125 µm, pregelatinised starch produced by subjecting moistened starch to mechanical pressure in order to rupture some or all of its starch granules and subsequent drying, talc, colloidal anhydrous silica, and magnesium stearate. This is an independent basis for patentability from the stabilising effect of microcrystalline cellulose having a mean particle size of less than 125 µm.

There were no findings in the final Office Action that would be relevant to these specific amounts. In this respect, only MITRA discloses specific preparation containing levothyroxine sodium but they appear to be only the following unit dose forms: 25 µg, 100 mg and 300 mg of the active ingredient. No unit dose forms of the required 0.0425-0.0575 mg ("50 µg tablet") or 0.085-0.115 mg ("100 µg tablet") levothyroxine sodium are

taught or suggested. Therefore, claims 18-19 would not have been obvious from MITRA in view of MSDS, EUROPEAN PHARMACOPOEIA, and FRANZ.

For the reasons explained above, it is submitted that the claimed invention is not obvious over the cited documents. The limitation of the pending claims to microcrystalline cellulose having a mean particle size of less than 125 μm is sufficient to distinguish over the cited documents so other incorrect allegations about their disclosures are not disputed here, but the opportunity to dispute them in the future is reserved. In particular, arguments in previous responses about the nonobviousness of (1) substituting pregelatinised starch for unmodified starch and (2) requiring a water content of 3-6% are maintained for the future purpose of appealing this rejection.

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinarily skill in the art when this invention was made.

*Conclusion*

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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